

Applicant's Remarks

As a preliminary matter, Applicant notes the claims have not been currently amended.

As a further preliminary matter, the Examiner's attention is directed to the Rule 132 Declaration of Kiyoshi Kawamura included herewith, as part of this response.

As a summary of the Office Action, Applicant was rejected under 35 USC 103(a) over U. S. 6,951,867 (hereinafter "Katsu") in view of Suzuki et al., *Chem. Pharm. Bull.*, 48(12), 2003-2008 (2000) (hereinafter "Suzuki"). Applicant was further rejected under 35 USC 103(a) over JP 09-194374 (Ouchi) in view of EP 0382687 (Micheletti).

Reconsideration and withdrawal of the rejections is respectfully requested in light of the comments herein and in view of the Rule 132 Declaration of Kiyoshi Kawamura.

Claims 15-21, 24 and 25 were rejected for obviousness over Katsu in view of Suzuki. The rejection is traversed on the ground that it is impermissibly based on hindsight. Applicant's position is that the rejection could only be made by using Applicant's specification in impermissible hindsight fashion, as a template to enable the Examiner to assemble Applicant's compounds by picking isolated pieces from different references and then reassembling them using Applicant's specification as a guide.

In particular, Applicant notes that Katsu has a completely different (imidazopyridine) central ring system from Applicant's quinolone carboxylic acid system. One of ordinary skill in the art interested in quinolone carboxylic acid compounds would accordingly dismiss Katsu out of hand as irrelevant.

Similarly, although Suzuki discloses, *inter alia*, compounds having a quinolonecarboxamide ring system, there are many other differences between Suzuki and the instant invention. For example, Suzuki lacks Applicant's "A" alkylene moiety. In addition, Suzuki discloses nothing resembling Applicant's B-R³ group, much less the fact that more than one R³ moiety can be present. Clearly, Suzuki's side chain is different from and non-overlapping with Applicant's side chain, and Suzuki contains no suggestion for modifying his compounds in a manner that would render the instant invention obvious. Applicant respectfully submits that one of ordinary skill in the art would not look to the totally different compounds of Katsu and, in isolation, arbitrarily single out any of Katsu's side chains.

Further, neither Katsu nor Suzuki contains anything corresponding to or suggestive of Applicant's R² substituent. The Examiner contended that this difference is *prima facie* obvious "...because it is well established that the substitution of a methyl for hydrogen on a known compound is not a patentable modification absent unexpected or

unobvious results". Applicant respectfully disagrees with the Examiner's comments because the instant claims are not directed to known compounds in which the substitution of methyl for hydrogen represents the only difference. Rather, Applicant's implementation of a substituent at R² represents another distinct difference in addition to those reviewed above. When considering the issue of obviousness, this additional difference must be weighed along with all of the others in judging whether Applicant's compounds, which have multiple differences including the R² substituent difference, are obvious as a whole.

Applicant submits that the answer to whether their invention is obvious over Katsu/Suzuki is "no". The differences between Applicant's claims and Katsu/Suzuki are manifold and neither Katsu nor Suzuki provides even remote guidance as to whether, how or why, and which differences among all those that are possible at various positions on the rings and side chains should or could be implemented, much less whether and how biological activity would be affected. Applicant's compounds are no more obvious than any other compounds that could be imagined by choosing a ring system from a first reference (Suzuki), by choosing from among numerous side chains in a second reference (Katsu), and by then permuting and splicing them, but with no guidance in either reference as to whether, how, or why this should be done, and which changes are better than others so far as their effect(s) on biological activity. Applicant respectfully submits that the only way to arrive at their compounds, once having seen them, is by choosing from among a plethora of variables and then assembling them using Applicant's claims as a guide. That, however, is the essence of a hindsight rejection which is well accepted as being legally impermissible.

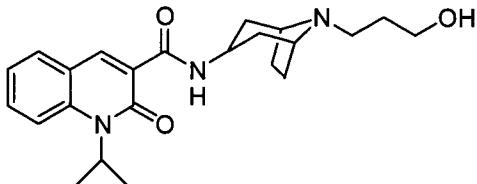
Applicant draws further attention to *Takeda v. Alphapharm*, 492 F.3d 1350 (2007) in which, referring to the KSR case (*KSR International Company v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385 (2007)), the Federal Circuit stated that "the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new inventions does in an obviousness determination. Applicant notes that neither Katsu nor Suzuki provides such reasoning.

Claims 15-20, 24 and 25 were rejected under 35 USC 103(a) over JP 09-194374 (referred to herein as "Ouchi") in view of EP 0382687 (referred to herein as "Micheletti"). Applicant respectfully submits that the basis for the rejection is not agreed with. However, in an effort to expedite prosecution, Applicant submits the Rule 132 Declaration of Kiyoshi Kawamura, one of the inventors in the instant application, herewith. Applicant respectfully submits that their claims define patentable subject matter in light of the evidence and testimony provided in the Declaration.

The Declaration presents data supporting that Applicant's compounds are generally unexpectedly superior to what one would expect based on Ouchi. In particular, Declarant Kawamura testifies as to the data presented in the Table in paragraph 4, the Table being reproduced below for convenience. Declarant Kawamura notes the table was obtained in accordance with the procedure titled as "Human 5-HT₄ binding" disclosed starting at page 19 and the procedure titled as "Human dofetilide binding" disclosed starting at page 22. Results are summarized as follows.

Compound	h5-HT ₄ (nM) (=A)	dofetilide (μM) (=B)	Therapeutic Index based on dofetilide/5-HT ₄ ratio (B/A)
Compound A	40.5	1.55	38
Example 2	6.17	1.9	308
Example 6	5.3	1.8	340
Example 7	5.24	5.83	1113
Example 8	5.2	5.35	1029
Example 11	7.56	6.61	874
Example 12	8.54	4.39	514

Applicant notes that compound A is the following compound,



which is Ouchi's compound as claimed in claim 2 of JP 09-194374. Declarant Kawamura testifies that the results presented in the Table clearly demonstrate that the compounds of the instant invention generally possess a surprisingly superior Therapeutic Index (TI), and in addition possess greatly improved 5-HT₄ activity. There is no reason based on Ouchi, and certainly none based on Micheletti, to expect that Applicant's compounds would display such an improvement in Therapeutic Index and improved 5-HT₄ activity. The Examiner is accordingly respectfully requested to consider the evidence presented in the Declaration and to withdraw the rejection based on Ouchi in view of Micheletti.

In view of the foregoing comments and the Declaration of Kiyoshi Kawamura included herewith, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

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Respectfully submitted,

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